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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/688,254	10/13/2000	Harry M. Meade	GTC-43	9900
31904	7590	04/20/2005	EXAMINER	
GTC BIOTHERAPEUTICS, INC. 175 CROSSING BOULEVARD, SUITE 410 FRAMINGHAM, MA 01702			QIAN, CELINE X	
			ART UNIT	PAPER NUMBER
			1636	

DATE MAILED: 04/20/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

## Office Action Summary

**Application No.**

09/688,254

**Applicant(s)**

MEADE ET AL

**Examiner**

Celine X. Qian Ph.D.

**Art Unit**

1636

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 24 March 2005.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 21-25, 27-30 and 37-43 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 21-25, 27-30 and 37-43 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 13 November 2002 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
  - ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- |  |   |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)   | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)                                   | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)             |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)<br>Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____  |

### **DETAILED ACTION**

Claims 21-25, 27-30, 37-43 are pending in the application.

This Office Action is in response to the Amendment filed on 3/24/05.

#### ***Continued Examination Under 37 CFR 1.114***

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 3/24/05 has been entered.

#### ***Response to Amendment***

The rejection of claims 9, 10, 20 and 26 under 35 U.S.C. 112 1<sup>st</sup> paragraph is moot in light of Applicant's cancellation of the claims.

The rejection of claims 5, 6, 8-10 under 35 U.S.C. 103 (a) is moot in light of Applicant's cancellation of the claims.

Claims 21-25, 27-30, 37-43 stand rejected under 35 U.S.C. 112 1<sup>st</sup> paragraph (written description) for reasons set forth of the record mailed on 1/29/04 and further discussed below.

Claims 37-42 are rejected under 35 U.S.C. 112 1<sup>st</sup> paragraph (new matter) for reasons discussed below.

Claims 21-25, 27-30 and 43 are rejected under 35 U.S.C. 103 (a) for reasons discussed below.

Claim 25 is rejected under 35 U.S.C. 112 2<sup>nd</sup> paragraph for reasons discussed below.

***Response to Arguments***

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 21-25, 27-30 and newly added claims 37-43 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicants did not make any argument with regard to this rejection. Applicants assert that cancellation of claims 20, 26, and 31-36 overcomes the new matter rejection, thus the remaining claims in better condition for allowance.

This argument has been fully considered but deemed unpersuasive. The claims are rejected for lack of sufficient written description “functional fragment thereof” or “chemically functional fragment thereof” of the claimed antibody, receptor, and ligand for reasons discussed in the previous office actions. Since Applicants have not provided arguments and/or evidence that such genus is adequately described, this rejection is thus maintained. Claims 27-30 also recites “chemically functional fragments” of antibody and CBD, they are rejected for same reasons set forth above. In addition, newly added claims 37-43 depend on claims 21 or 27, they are rejected for same reason as applied to claims 21 and 27.

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Newly added claims 37-42 are also rejected for containing new matter. The instant specification does not disclose that the multivalent polypeptide is used in an ELISA format, the reaction mixture is semi-solid, and the target polypeptide is purified to more than 90% purity. Therefore, the claims are rejected for constitute new matter.

***Claim Rejections - 35 USC § 103***

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 21-25, 27-30 and 43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cheng et al. (5,981,714), in view of Radford et al. (5,955,270), Scharwz et al. (5,719,269), Wagner et al. (6,329,209), Meade et al. (5,750,172), and Nuijens et al. (1997, JBC, Vol.272, No.13, pp.8802-8807).

Cheng et al. teach a method of purifying a target polypeptide by using antibody which binds to a matrix. Cheng et al. also teach that the standard method for such purification consists preparation of antibody-matrix, binding an antigen to the antibody-matrix, removing contaminants by washing, and elution of the antigen (see col. 7 line 56 through line 12, col. 8). However, Cheng et al. does not teach that the antibody is made transgenically. Cheng et al. do not teach that the target polypeptide is an antibody. Cheng et al. do not teach that the antibody used to purify the polypeptide having either protein L or CBD. Cheng et al. do not teach that the target polypeptide is a receptor or a ligand.

Schwartz et al. teach that method of purifying an antibody by using immobilized ligand immobilized to a matrix is well known in the art (see col.1, 4<sup>th</sup> paragraph). Schwartz et al. also

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teach that bacterial protein A, G and L are commonly used in this method because they specifically bind to IgG antibodies (see col. 1 through col. 2, 2<sup>nd</sup> paragraph).

Radford et al. teach that by adding the cellulose binding domain to an expression construct makes it easier for the subsequent purification (col. 2 line 59 through col.3 lines 13). Radford et al. further teach a method of purifying cellobiohydrolase-1 comprising the cellulose-binding domain can be used to bind to a cellulose matrix and washing off other components, thereby purifying said enzyme.

Wagner et al. teach that a method of capturing proteins to an array chip by using capturing agents that are attached to the chip (col.3). Wagner et al. also teach that the capturing agents can bind a protein to itself in a specific manner. They include antibodies, wherein the binding partner is antigen, and receptors, wherein their binding partner is ligand (see col.4, lines 48-67).

Nuijens et al. teach the expression and characterization of the recombinant human lactoferrin secreted in milk of transgenic mice. Nuijens et al. teach that the transgenically produced lactoferrin is very similar to the natural lactoferrin, and exerts same anti-bacterial and anti-inflammatory activities in vivo.

Meade et al. teach the production of a number of recombinant proteins including TPA, urokinase, growth hormones and immunoglobulins in the milk of transgenic non-human mammal (see col.3, 3<sup>rd</sup> paragraph, and Examples 1-3).

Based on the combination of teaching of Cheng et al. (5,981,714), Scharwz et al. (5,719,269), and Nuijens et al. (1997, JBC, Vol.272, No.13, pp.8802-8807), it would have been obvious to one of ordinary skill in the art to develop a method of purifying target polypeptide

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either from milk of a transgenic mammal or other mixtures by contacting the target polypeptide with a transgenically produced multivalent binding polypeptide, (for example, the antibody that is capable of binding to a matrix taught by Cheng et al.) having a first bindable epitope which binds the target polypeptide (for example, the antigen taught by Cheng et al.) and a second bindable epitope which binds a matrix, and subsequent elution of the polypeptide from the matrix. The ordinary artisan would have been motivated to do so because a transgenically produced polypeptide is structurally same as the natural occurring polypeptide as demonstrated by Nuijen et al. Further, Meade et al. teach the generation of recombinant immunoglobulins in the milk of the transgenic non-human mammal. At the time of filing, the skill of art in producing recombinant protein in milk of transgenic mammal is high. Absent evidence to the contrary, one of ordinary skill in the art would have reasonable expectation of success to develop such a purification method using the multivalent polypeptide that is produced by a transgenic mammal. Therefore, the invention would have been *prima facie* obvious to one of ordinary skill of art at the time the invention was made.

It would also have been obvious to one of ordinary skill of art to use CBD as the second binding moiety of the multivalent polypeptide based on the teaching of Cheng et al. (5,981,714), Scharwz et al. (5,719,269), Radford et al. (5,955,270), and Nuijens et al. (1997, JBC, Vol.272, No.13, pp.8802-8807). The ordinary artisan would have been motivated to do so because Radford et al. teach that CBD binds to cellulose matrix and makes it easier to purify proteins comprising this domain. Since the nucleic acid sequence encoding those binding domains are known, attaching them to a polypeptide would have been routine experimentation at the time of filing. Absent evidence from the contrary, the ordinary skill of art would have reasonable

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expectation of success to produce a multivalent polypeptide with CBD domain as second binding moiety transgenically and use it to purify a target polypeptide such as IgGs. Therefore, the invention would have been *prima facie* obvious to one of ordinary skill of art at the time the invention was made.

It would also have been obvious to one of ordinary skill of art to use a receptor as the first binding moiety when the target polypeptide is a ligand or vice versa based on the teaching of Cheng et al. (5,981,714), Wagner et al. (6,329,209), and Nuijens et al. (1997, JBC, Vol.272, No.13, pp.8802-8807). One of ordinary skill of art would have been motivated to do so because Wagner et al. teach that receptor-ligand and antigen-antibody interaction is specific for protein capturing agent to bind to the ligand in a biological sample. Many receptor and ligand have been cloned and characterized at the time of filing. One ordinary skill of art would have plenty of information to choose receptor when a ligand needs to be purified and vice versa. Absent evidence from the contrary, one of ordinary skill of art would have reasonable expectation to transgenically produce a multivalent polypeptide with a binding moiety from either a ligand or a receptor. Therefore, the invention would have been *prima facie* obvious to one of ordinary skill of art at the time the invention was made.

Applicants did not provide and arguments regard this rejection. Therefore, this rejection is maintained for reasons set forth in the previous office actions and above.

***New Grounds of Rejection Necessitated by Applicant's Amendment***

***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.



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Claim 25 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The recitation of "a second non-human transgenic mammal" renders the claim indefinite because there is no first transgenic mammal recited in the claim. It is unclear which transgenic mammal Applicants are referring to.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Celine X. Qian Ph.D. whose telephone number is 571-272-0777. The examiner can normally be reached on 9:30-6:00 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel Ph.D. can be reached on 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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